



Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial

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Summary

Background Previous trials have shown that anti-EGFR monoclonal antibodies can improve clinical outcomes of patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN). We assessed the efficacy and safety of panitumumab combined with cisplatin and fluorouracil as first-line treatment for these patients.

Methods This open-label phase 3 randomised trial was done at 126 sites in 26 countries. Eligible patients were aged at least 18 years; had histologically or cytologically confirmed SCCHN; had distant metastatic or locoregionally recurrent disease, or both, that was deemed to be incurable by surgery or radiotherapy; had an Eastern Cooperative Oncology Group performance status of 1 or less; and had adequate haematological, renal, hepatic, and cardiac function. Patients were randomly assigned according to a computer-generated randomisation sequence (1:1; stratified by previous treatment, primary tumour site, and performance status) to one of two groups. Patients in both groups received up to six 3-week cycles of intravenous cisplatin (100 mg/m² on day 1 of each cycle) and fluorouracil (1000 mg/m² on days 1–4 of each cycle); those in the experimental group also received intravenous panitumumab (9 mg/kg on day 1 of each cycle). Patients in the experimental group could choose to continue maintenance panitumumab every 3 weeks. The primary endpoint was overall survival and was analysed by intention to treat. In a prospectively defined retrospective analysis, we assessed tumour human papillomavirus (HPV) status as a potential predictive biomarker of outcomes with a validated p16-INK4A (henceforth, p16) immunohistochemical assay. Patients and investigators were aware of group assignment; study statisticians were masked until primary analysis; and the central laboratory assessing p16 status was masked to identification of patients and treatment. This trial is registered with ClinicalTrials.gov, number NCT00460265.

Findings Between May 15, 2007, and March 10, 2009, we randomly assigned 657 patients: 327 to the panitumumab group and 330 to the control group. Median overall survival was 11·1 months (95% CI 9·8–12·2) in the panitumumab group and 9·0 months (8·1–11·2) in the control group (hazard ratio [HR] 0·873, 95% CI 0·729–1·046; *p*=0·1403). Median progression-free survival was 5·8 months (95% CI 5·6–6·6) in the panitumumab group and 4·6 months (4·1–5·4) in the control group (HR 0·780, 95% CI 0·659–0·922; *p*=0·0036). Several grade 3 or 4 adverse events were more frequent in the panitumumab group than in the control group: skin or eye toxicity (62 [19%] of 325 included in safety analyses *vs* six [2%] of 325), diarrhoea (15 [5%] *vs* four [1%]), hypomagnesaemia (40 [12%] *vs* 12 [4%]), hypokalaemia (33 [10%] *vs* 23 [7%]), and dehydration (16 [5%] *vs* seven [2%]). Treatment-related deaths occurred in 14 patients (4%) in the panitumumab group and eight (2%) in the control group. Five (2%) of the fatal adverse events in the panitumumab group were attributed to the experimental agent. We had appropriate samples to assess p16 status for 443 (67%) patients, of whom 99 (22%) were p16 positive. Median overall survival in patients with p16-negative tumours was longer in the panitumumab group than in the control group (11·7 months [95% CI 9·7–13·7] *vs* 8·6 months [6·9–11·1]; HR 0·73 [95% CI 0·58–0·93]; *p*=0·0115), but this difference was not shown for p16-positive patients (11·0 months [7·3–12·9] *vs* 12·6 months [7·7–17·4]; 1·00 [0·62–1·61]; *p*=0·998). In the control group, p16-positive patients had numerically, but not statistically, longer overall survival than did p16-negative patients (HR 0·70 [95% CI 0·47–1·04]).

Interpretation Although the addition of panitumumab to chemotherapy did not improve overall survival in an unselected population of patients with recurrent or metastatic SCCHN, it improved progression-free survival and had an acceptable toxicity profile. p16 status could be a prognostic and predictive marker in patients treated with panitumumab and chemotherapy. Prospective assessment will be necessary to validate our biomarker findings.

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Introduction

Platinum-based combination chemotherapy regimens can be used to treat patients with incurable locoregionally recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN).¹ Although these regimens lead to tumour responses in about 10–35% of patients, median survival is less than 1 year and the effects on patients' quality of life are unknown.^{2–6}

Dysregulation of the EGFR signalling pathway plays a part in the development and progression of SCCHN.^{7,8} Clinical trials^{6,9} have shown that addition of anti-EGFR monoclonal antibodies to chemotherapy improves clinical outcomes in patients with recurrent or metastatic SCCHN. In a randomised phase 3 study in the USA,⁶ more patients in the group given cisplatin plus cetuximab responded than in the group receiving cisplatin plus placebo; and in a randomised phase 3 study (EXTREME) in Europe,⁹ addition of cetuximab to cisplatin and fluorouracil or to carboplatin and fluorouracil improved overall survival.

Human papillomavirus (HPV) DNA has been detected in up to two-thirds of oropharyngeal SCCHN tumours in patients presenting with locoregionally advanced disease.^{10,11} Patients with locoregionally advanced HPV-positive oropharyngeal SCCHN who are treated with radiotherapy with or without chemotherapy have a better outlook than do HPV-negative patients.^{11–16} However, the global prevalence and prognostic effect of HPV in patients with recurrent or metastatic SCCHN arising from the oropharynx, oral cavity, larynx, and hypopharynx is not well understood, particularly in the clinical trial setting. HPV-positive and HPV-negative SCCHN tumours differ in terms of biology, histology, genetic alterations, and prognosis.^{11,13,17,18} HPV-positive SCCHN tumours are characterised by the presence of high-risk HPV DNA (most commonly HPV 16) and the co-expression of the viral oncoproteins E6 and E7, which modulate expression of key cellular proteins (such as the tumour suppressor p53 and retinoblastoma tumour-suppressor protein), leading to upregulated expression of the cyclin-dependent kinase inhibitor p16-INK4A (henceforth, p16).^{10,18,19} How HPV status affects the outlook of patients with recurrent or metastatic disease, or their response to treatment, is unknown. Some studies^{20–24} have suggested interactions between HPV and the EGFR signalling pathway. Therefore, HPV status (as assessed by p16 immunohistochemistry of formalin-fixed paraffin-embedded samples) might affect outcomes during anti-EGFR treatment.

Panitumumab is a fully human anti-EGFR monoclonal antibody that is used both as a single agent and combined with chemotherapy for treatment of metastatic colorectal cancer.²⁵ Preclinical data for SCCHN cell lines and xenografts showed more antitumour activity with panitumumab plus radiotherapy than with radiotherapy alone,²⁶ and phase 1 response data for panitumumab plus chemoradiotherapy have suggested that additional

investigation of panitumumab in SCCHN is warranted.²⁷ In the Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer (SPECTRUM), we compared panitumumab plus cisplatin and fluorouracil with chemotherapy alone as first-line treatment for recurrent or metastatic SCCHN. Additionally, we investigated the relative effect of treatment with panitumumab combined with chemotherapy in patients with recurrent or metastatic SCCHN who do (p16 positive) or do not (p16 negative) express p16.

Methods

Study design and participants

This open-label phase 3 randomised trial was done at 126 sites in 26 countries. Eligible patients were aged at least 18 years; had histologically or cytologically confirmed SCCHN; had distant metastatic or locoregionally recurrent disease, or both, that was deemed to be incurable by surgery or radiotherapy; had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less; and had adequate haematological, renal, hepatic, and cardiac function. Patients who had received primary radiation therapy were eligible when locoregional recurrence was in the field of radiation and occurred at least 6 months after therapy completion, or when it was outside the field of radiation and occurred at least 3 months after therapy completion. Patients were excluded if they had received previous systemic chemotherapy for recurrent or metastatic SCCHN (unless part of multimodality treatment for locoregionally advanced SCCHN completed more than 6 months before study entry); had another primary cancer with treatment within 2 years of randomisation; had nasopharyngeal carcinoma or CNS metastases; had undergone major surgery in the previous 4 weeks or minor surgery in the previous 2 weeks; or had received previous anti-EGFR treatment (unless part of initial curative multimodality therapy).

The study protocol was approved by independent ethics committees at each participating centre. All participants provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to one of two groups according to a computer-generated randomisation sequence (provided by an external vendor [ICON Clinical Research, North Wales, PA, USA]) with an automated interactive voice response system. Randomisation was stratified by previous treatment (newly diagnosed or previously untreated *vs* recurrent disease), primary tumour site (combined hypopharynx and oral cavity *vs* combined oropharynx and larynx), and ECOG performance status (0 *vs* 1). Double-blind treatment assignment was not possible because of the characteristic rash associated with EGFR inhibitors, including monoclonal antibodies such as panitumumab.²⁸ Patients and investigators were aware of group assignment, and study statisticians were masked

until the primary analysis. Pathologists doing p16 immunohistochemical assays were masked to patient identification and treatment.

Procedures

Patients in the panitumumab group received cisplatin and fluorouracil plus panitumumab, and those in the control group received cisplatin and fluorouracil alone. All patients received 100 mg/m² intravenous cisplatin on day 1 of a 3-week cycle, and 1000 mg/m² intravenous (continuous) fluorouracil infusion on days 1–4 of each cycle. Carboplatin (target area under the curve by the Calvert formula 5 mg/mL per min) could be permanently substituted for cisplatin when patients had creatinine clearance of less than 50 mL/min or grade 2 neurological toxicity (eg, sensory or motor neuropathy and ototoxicity). Patients in the panitumumab group received 9 mg/kg intravenous panitumumab on day 1 of each cycle immediately before receiving chemotherapy.

Treatment continued until disease progression or for a maximum of six 3-week cycles. Patients who discontinued one study drug could receive the remaining drugs until completion of six cycles, disease progression, intolerable toxicity, or study withdrawal. Protocol-specified dose modifications and interruptions of study drugs were allowed when patients experienced toxicity (appendix). Patients in the panitumumab group who had not had disease progression after six cycles could choose to receive panitumumab until disease progression, intolerable toxicity, or study withdrawal.

Tumour response was assessed by CT or MRI at baseline and then every 6 weeks until disease progression. As per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.0),²⁹ complete or partial tumour responses were confirmed at least 4 weeks after the initial response assessment. Patients who discontinued treatment were followed up to obtain data for safety (30 days after the last treatment), survival (every 3 months until 3 years after the last patient underwent randomisation), and subsequent treatment for SCCHN (every 3 months until 3 years after the last patient underwent randomisation).

Adverse events occurring during the study were graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).³⁰ Clinical and laboratory assessments were done at screening, on day 1 of each cycle, and during safety follow-up. Serum samples for anti-panitumumab antibody analysis were obtained from patients in the panitumumab group before receiving infusions on day 1 of cycles 1 and 5, every 6 months thereafter, and at the safety follow-up visit. The serum samples were analysed as described previously.³¹

Core biopsies (1 mm) from available formalin-fixed paraffin-embedded SCCHN tumour blocks (primary or metastatic sites) were obtained, sectioned, reviewed by a pathologist, and used to construct a tumour microarray.

In sites where blocks were not submitted, tissue slides were assessed. An immunohistochemical assay (p16INK4a Histology Kit, CINtec, Roche mtm laboratories AG, Heidelberg, Germany) that has been validated for testing of cervical cancer samples and qualified for assessment of p16 expression in SCCHN samples³² was used to determine tumour HPV status according to a prespecified plan. Tumour p16 expression was detected with the Clone E6H4 monoclonal antibody (Roche mtm laboratories AG, Heidelberg, Germany) and stained with a Nemesis Autostainer and diaminobenzidine secondary detection kit (Dako, Carpinteria, CA, USA). Samples were judged to be p16 positive when they had strong and diffuse nuclear and cytoplasmic staining in at least 10% of tumour cells;³² all other patients were defined as p16 negative. The immunohistochemical assay success rate was more than 99%.

Statistical analysis

The primary endpoint was overall survival (time from randomisation to death); patients who had not died at the time of the primary analysis were censored on the date that they were last known to be alive. An estimated 470 deaths would provide 90% power to detect a hazard ratio (HR) of 0.7407, with an α of 0.05. With the assumptions that median overall survival in the control group would be 8.7 months (estimate based on assessment of clinical experience with platinum-based chemotherapy in recurrent or metastatic SCCHN) and an exponential distribution for overall survival, this HR would translate into a 35% relative and 3-month absolute

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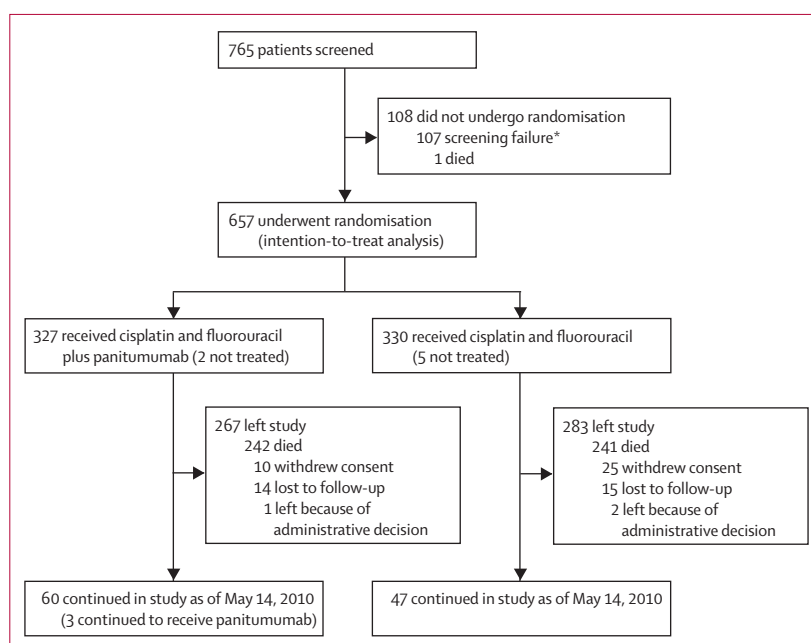


Figure 1: Trial profile

*34 did not meet disease-related eligibility criteria, 20 laboratory failure, 10 timing or toxic effects from previous treatment, 2 inadequate or inappropriate previous treatment, 1 withdrew consent, and 40 for other reasons.

increase in median overall survival. We estimated that 650 patients would have to undergo randomisation in 20 months and have about 18 months of follow-up. The maximum planned study duration was 56 months.

Secondary endpoints were progression-free survival (PFS; time from randomisation to disease progression or death), proportions of patients who achieved an objective response (complete and partial responses combined),

duration of response (DOR; time from first confirmed objective response to disease progression, per RECIST), time to response (TTR; time from randomisation to first confirmed objective response), and safety.

The primary analysis of overall survival and PFS was done by intention to treat. We assessed numbers of objective responses, TTR, and DOR in patients with at least one one-dimensionally measurable lesion at baseline, per RECIST. All randomly assigned patients who received at least one dose of panitumumab or chemotherapy were included in the safety analysis. An independent data monitoring committee did interim safety analyses on a roughly annual basis during the treatment phase.

We did between-group comparisons of overall survival and PFS with log-rank tests stratified by randomisation factors. When the difference in overall survival was not significant, all other p values were descriptive only. We estimated HRs and 95% CIs for overall survival and PFS with a Cox model stratified by randomisation factors. We used the Cochran-Mantel-Haenszel method³³ to assess the association between treatment group (panitumumab plus chemotherapy vs chemotherapy alone) and objective response (yes vs no), while controlling for randomisation stratification factors. We used the Wilson score method³⁴ with continuity correction to calculate a 95% CI for the difference in numbers of objective responses. For patients with an objective response, we estimated DOR with the Kaplan-Meier method, and assessed TTR with descriptive statistics. We did post-hoc analyses to assess differences in adverse events between groups with Fisher's exact test, with no correction for multiple comparisons. Analyses were done in SAS (version 9.2).

We assessed all patients in the intention-to-treat dataset with formalin-fixed paraffin-embedded tumour samples for p16 status. We used data from the primary analysis in the retrospective analysis of overall survival and PFS by tumour p16 status. We used an unstratified univariate Cox model for comparisons of overall survival and PFS between p16 groups, and unstratified log-rank tests and Cox models to assess the treatment effect within p16 groups.

This study is registered with ClinicalTrials.gov, number NCT00460265.

Role of the funding source

The study sponsor was involved in study design, in collaboration with the corresponding author and members of the SPECTRUM steering committee; provision of access to the raw data to the study biostatistician (ZP); data management; prespecified statistical analyses; and data interpretation. JBV and BB led development of the report; all authors (some of whom are employed by the funder) participated in the writing of the report. The study sponsor funded medical writing assistance. The corresponding author had full access to

| | Panitumumab group (n=327) | Control group (n=330) |
|---|---------------------------|-----------------------|
| Men | 283 (87%) | 287 (87%) |
| Women | 44 (13%) | 43 (13%) |
| Geographical region | | |
| North America | 24 (7%) | 25 (8%) |
| Western Europe | 101 (31%) | 116 (35%) |
| Asia-Pacific | 54 (17%) | 42 (13%) |
| South America | 25 (8%) | 31 (9%) |
| Eastern Europe | 123 (38%) | 116 (35%) |
| Ethnic origin | | |
| White | 268 (82%) | 271 (82%) |
| Black | 4 (1%) | 2 (1%) |
| Hispanic | 13 (4%) | 12 (4%) |
| Asian | 25 (8%) | 30 (9%) |
| Japanese | 13 (4%) | 7 (2%) |
| Other* | 4 (1%) | 8 (2%) |
| Age (years) | 58 (53–63) | 59 (53–64) |
| <65 | 268 (82%) | 256 (78%) |
| ≥65 | 59 (18%) | 74 (22%) |
| Eastern Cooperative Oncology Group performance status | | |
| 0 | 98 (30%) | 98 (30%) |
| 1 | 227 (69%) | 228 (69%) |
| 2† | 2 (1%) | 4 (1%) |
| Duration of disease (months) | 15.0 (9.6–26.2) | 15.9 (10.1–32.5) |
| Involuntary weight loss in the previous 6 months | | |
| 0–5% | 27 (8%) | 28 (8%) |
| >5% | 60 (18%) | 68 (21%) |
| None or missing | 240 (73%) | 234 (71%) |
| Primary tumour site | | |
| Oropharynx | 86 (26%) | 96 (29%) |
| Hypopharynx | 52 (16%) | 37 (11%) |
| Larynx | 100 (31%) | 95 (29%) |
| Oral cavity | 89 (27%) | 102 (31%) |
| Extent of disease | | |
| Locoregional recurrence only | 143 (44%) | 126 (38%) |
| Distant metastatic | 119 (36%) | 123 (37%) |
| Distant metastatic and locoregionally recurrent | 65 (20%) | 81 (25%) |
| Primary tumour histological type | | |
| Well differentiated | 63 (19%) | 63 (19%) |
| Moderately differentiated | 133 (41%) | 123 (37%) |
| Poorly differentiated | 54 (17%) | 70 (21%) |
| Undifferentiated | 6 (2%) | 6 (2%) |
| Not otherwise specified/unknown | 71 (22%) | 68 (21%) |

(Continues on next page)

all data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 15, 2007, and March 10, 2009, we randomly assigned 657 patients to the two treatment groups (figure 1). Baseline characteristics were similar in the two groups (table 1). Seven patients did not receive treatment (figure 1); 325 patients in each group received at least one dose of panitumumab or chemotherapy and were included in safety analyses.

Of the 327 patients assigned to the panitumumab group, all discontinued chemotherapy (reasons given for discontinuation of each component; some patients counted more than once): 155 completed protocol-specified chemotherapy, 55 did not meet protocol-specified criteria (29 had creatinine clearance <50 mL/min; 26 had grade 2 or 3 neurotoxicity), 46 had disease progression, 45 had an adverse event, 36 died, 31 requested discontinuation, eight withdrew consent, six were non-compliant, four were lost to follow-up, one was ineligible, and 15 for other reasons. 324 patients discontinued panitumumab at any point while in the study: 144 had disease progression, 48 requested discontinuation, 43 had an adverse event, 41 died, eight withdrew consent, seven were non-compliant, five were lost to follow-up, one was ineligible, and 27 for other reasons. Of the 330 assigned to the control group, all discontinued chemotherapy: 128 completed protocol-specified chemotherapy, 76 did not meet protocol specified criteria (55 had creatine clearance <50 mL/min; 20 had grade 2 or 3 neurotoxicity; 1 had grade 4 neurotoxicity), 88 had disease progression, 47 had adverse event, 29 died, 16 requested discontinuation, 19 withdrew consent, five were non-compliant, two were lost to follow-up, one was ineligible, and 15 for other reasons.

At the time of the primary analysis on May 14, 2010, 550 patients had left the study: 483 had died, 35 had withdrawn their consent, 29 were lost to follow-up, and three left because of decisions made by the study oversight team. 153 patients in the panitumumab group and 147 patients in the control group received at least one subsequent treatment for SCCHN after discontinuation of protocol-specified treatment: 97 in the panitumumab group and 84 the control group received additional cytotoxic chemotherapy; 50 and 46 radiotherapy or surgery, or both; and 15 and 31 anti-EGFR monoclonal antibody therapy.

The median relative dose intensity of panitumumab during the study (proportion given of amount planned) was 91% (IQR 83–98). The median number of 3-week cycles in which panitumumab was given was five (three to eight). The median duration of panitumumab treatment was 18.3 weeks (9.3–26.9). At least one dose of panitumumab was withheld for 39 patients (12%). 126 patients (39%) in the panitumumab group were eligible to continue panitumumab after completing six cycles of chemotherapy

| | Panitumumab group (n=327) | Control group (n=330) |
|---|---------------------------|-----------------------|
| (Continued from previous page) | | |
| Previous treatment† | | |
| Chemotherapy or radiotherapy, or both | 267 (82%) | 263 (80%) |
| Chemotherapy | | |
| Platinum | 128 (39%) | 113 (34%) |
| Fluoropyrimidine | 52 (16%) | 44 (13%) |
| Taxane | 7 (2%) | 8 (2%) |
| Methotrexate | 9 (3%) | 6 (2%) |
| Other | 15 (5%) | 18 (5%) |
| Radiotherapy | 266 (81%) | 259 (78%) |
| Patients with locoregionally advanced disease | 189 (58%) | 187 (57%) |
| Surgery | 282 (86%) | 284 (86%) |

Data are n (%) or median (range). *Australian Aboriginal, or unknown or missing. †Enrolled patients with a performance status of 2 were protocol violations. ‡Previous treatment given as adjuvant or part of multimodality treatment in locoregionally advanced disease >6 months before randomisation.

Table 1: Baseline characteristics

and panitumumab. 95 patients (75% of those eligible; 29% of all patients in the panitumumab group) continued with panitumumab maintenance treatment, and went on to receive a median of three cycles (IQR two to eight) of panitumumab monotherapy. Panitumumab monotherapy varied by region (appendix).

The median relative dose intensity of cisplatin was 87% (IQR 75–97) in the panitumumab group and 85% (72–98) in the control group, and the median relative dose intensity of carboplatin was 95% (84–100) and 98% (86–100). The median number of cisplatin cycles was 4.0 (2.0–6.0) in the panitumumab group and 4.0 (2.0–5.0) in the control group. The median number of carboplatin cycles was 2.0 (2.0–4.0) in the panitumumab group and 4.0 (2.0–5.0) in the control group. The median duration of cisplatin treatment was 13.4 weeks (7.9–19.3) in the panitumumab group and 13.0 weeks (6.4–18.4) in the control group. Overall, 155 patients (24%; 69 [21%] in the panitumumab group; 86 [26%] in the control group) switched from cisplatin to carboplatin. Fewer patients in the panitumumab group (29 [42%]) than in the control group (52 [60%]) switched because of a creatinine clearance of less than 50 mL/min. The median time to switching from cisplatin to carboplatin for any reason was 64 days (IQR 34–106) in the panitumumab group and 77 days (43–106) in the control group.

The median relative dose intensity of fluorouracil was 89% (79–97) in the panitumumab group and 90% (79–99) in the control group. The median number of fluorouracil cycles was 5.0 (3.0–6.0) in the panitumumab group and 4.0 (2.0–6.0) in the control group. The median duration of fluorouracil treatment was 17.9 weeks (9.1–20.0) in the panitumumab group and 15.0 weeks (7.0–19.9) in the control group.

Median overall survival was 11.1 months (95% CI 9.8–12.2) in the panitumumab group and 9.0 months

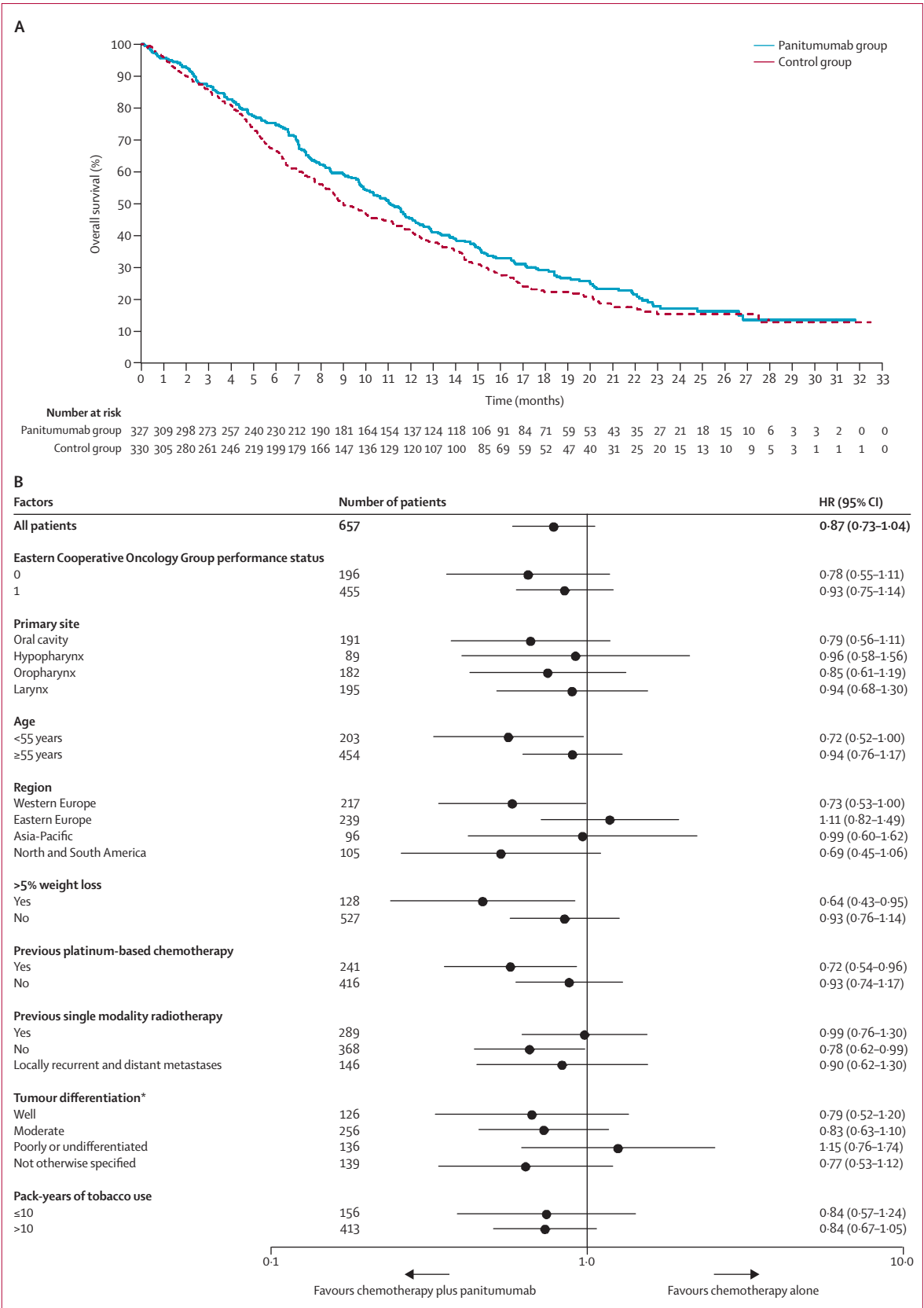


Figure 2: Kaplan-Meier curves by group (A) and subgroup analyses (B) for overall survival

*From local pathologist assessments on case report form.

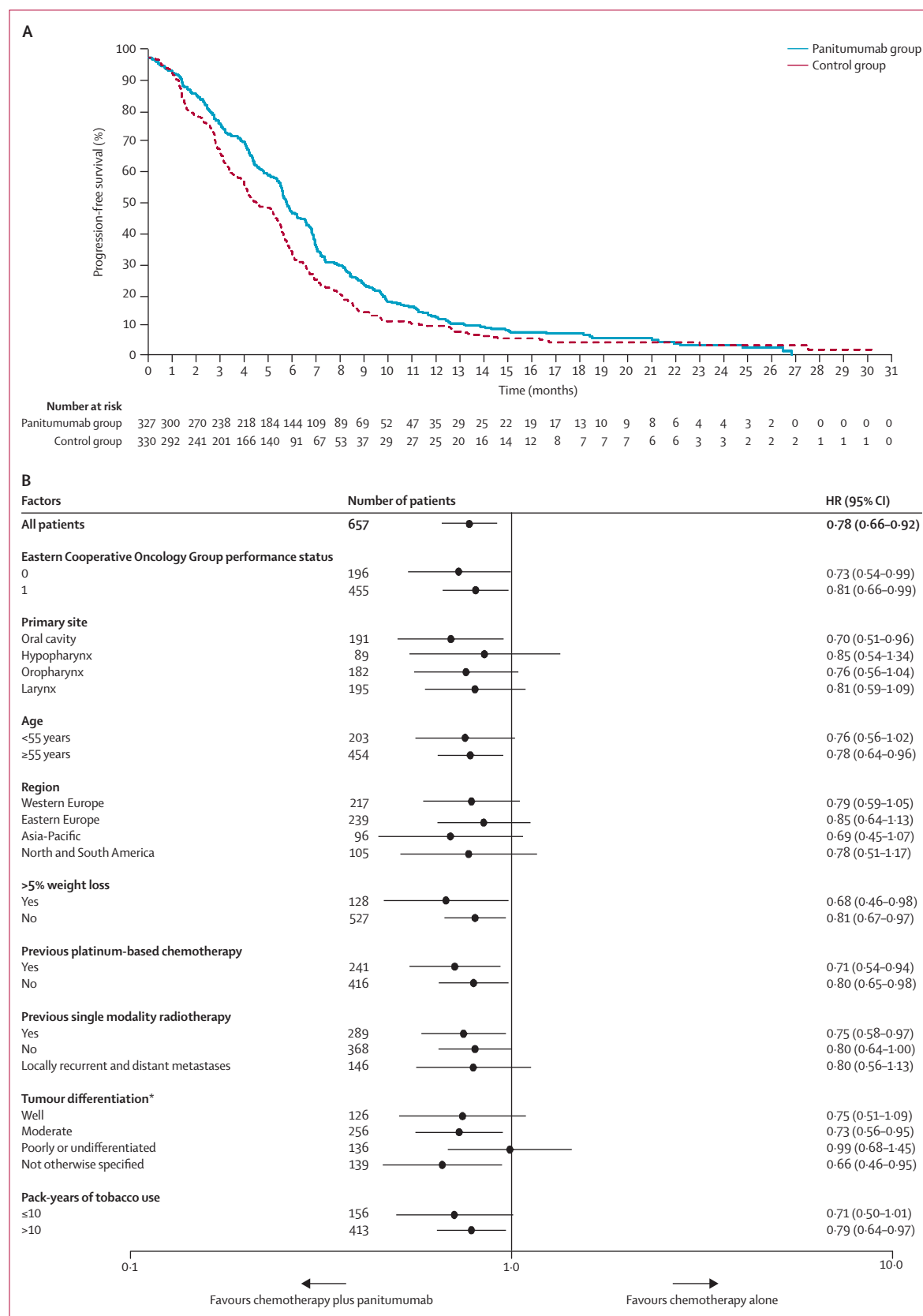


Figure 3: Kaplan-Meier curves by group (A) and subgroup analyses (B) for progression-free survival
 *From local pathologist assessments on case report form.

(8.1–11.2) in the control group ($p=0.1403$; HR 0.873, 95% CI 0.729–1.046; figure 2). Median follow-up was 44.0 weeks (IQR 21.0–75.0) in the panitumumab group and 35.0 weeks (16.0–66.0) in the control group. At the time of analysis, 242 patients (74%) in the panitumumab

group and 241 (73%) in the control group had died. We assessed the proportional hazards assumption between the treatment groups with graphical and numerical methods based on cumulative Martingale residuals and recorded no evidence of non-proportionality ($p=0.16$).

Median PFS was 5.8 months (95% CI 5.6–6.6) in the panitumumab group and 4.6 months (4.1–5.4) in the control group (HR 0.780, 95% CI 0.659–0.922; $p=0.0036$; figure 3). At the time of analysis, 290 patients (89%) in the panitumumab group and 275 (83%) in the control group had progressed or died. Sensitivity analyses suggested minor non-proportionality between treatment groups for PFS, but the results were consistent with those from the primary analysis (data not shown).

Overall, 566 patients had at least one baseline radiologically one-dimensionally measurable lesion. The proportions of participants who had an objective response (odds ratio 1.69, 95% CI 1.15–2.44; $p=0.0065$) or achieved disease control (odds ratio 1.84, 1.21–2.81; $p=0.0038$) were significantly higher in the panitumumab group than in the control group (table 2). Median DOR and median TTR were similar in the two groups (table 2).

Subgroup analyses of overall survival and PFS suggested that the results for overall survival (figure 2)

| | Panitumumab group (n=327) | Control group (n=330) |
|---|---------------------------|-----------------------|
| Included in tumour response analysis | 278 (85%) | 288 (87%) |
| Complete response | 5 (2%) | 5 (2%) |
| Partial response | 96 (35%) | 68 (24%) |
| Stable disease | 128 (46%) | 134 (47%) |
| Disease progression | 18 (6%) | 34 (12%) |
| Not assessable | 2 (1%) | 3 (1%) |
| Not done | 29 (10%) | 44 (15%) |
| Objective response (complete response and partial response) | 101 (36%, 31–42) | 73 (25%, 20–31) |
| Disease control (complete response, partial response, and stable disease) | 229 (82%, 77–87) | 207 (72%, 66–77) |
| Time to response (weeks) | 6.1 (5.9–11.0) | 6.7 (5.9–11.3) |
| Duration of response (months)* | 5.6 (4.8–6.2) | 5.7 (4.7–6.2) |

Data are n (%), n (%), 95% CI, or median (IQR). *Included only patients who had an objective response.

Table 2: Best overall response

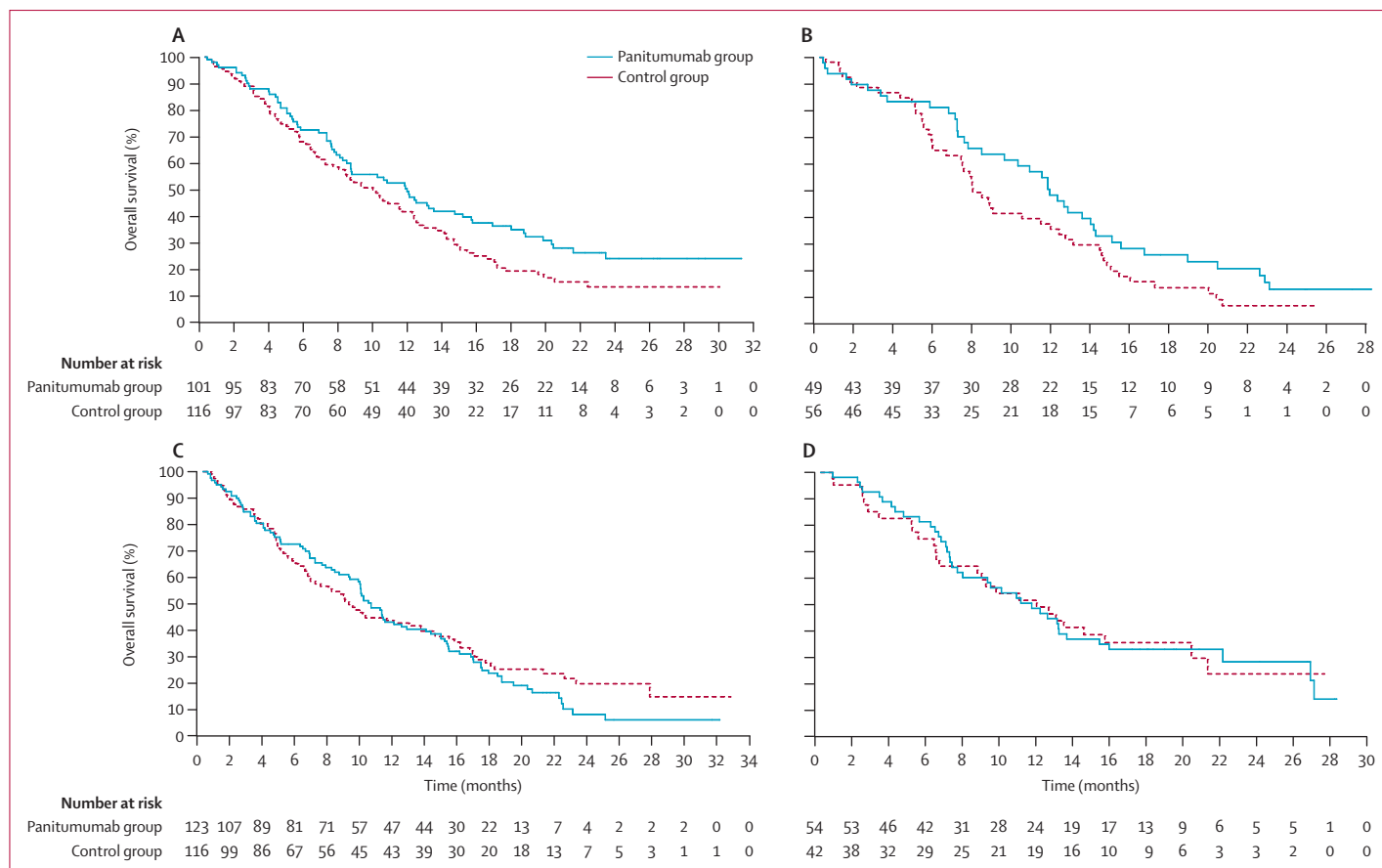


Figure 4: Overall survival by group in (A) western Europe, (B) North and South America, (C) eastern Europe, and (D) the Asia-Pacific region

| | Panitumumab group | | Control group | | Hazard ratio | Log-rank p value |
|-------------------------|-------------------|---------------------------|---------------|---------------------------|---------------------|------------------|
| | Died | Overall survival (months) | Died | Overall survival (months) | | |
| Western Europe | 69/101 (68%) | 11·7 (8·4–14·9) | 86/116 (74%) | 9·7 (7·4–12·1) | 0·727 (0·529–0·999) | 0·0478 |
| North and South America | 39/49 (80%) | 11·7 (8·2–13·9) | 47/56 (84%) | 7·8 (6·4–11·7) | 0·692 (0·450–1·065) | 0·0914 |
| Eastern Europe | 96/123 (78%) | 10·3 (9·6–12·6) | 81/116 (70%) | 9·0 (6·6–13·4) | 1·108 (0·823–1·492) | 0·5004 |
| Asia-Pacific region | 38/54 (70%) | 11·5 (7·4–15·1) | 27/42 (64%) | 11·7 (6·4–20·1) | 0·985 (0·600–1·616) | 0·9526 |

Data are n/N (%), median (95% CI), or hazard ratio (95% CI), unless otherwise stated.

Table 3: Overall survival in the two treatment groups by region

and PFS (figure 3) were consistent across most patient subgroups. Of note, median overall survival and HRs varied by geographic region (figure 4, table 3).

In univariate and multivariate analyses, several baseline covariates (such as previous platinum chemotherapy, ECOG performance status, weight loss in the previous 6 months, and disease stage) were significantly associated with overall survival (appendix). The effect of panitumumab in the multivariate model (HR 0·875, 95% CI 0·731–1·048; $p=0·146$) was consistent with that in the primary analysis (appendix).

Grade 3 or 4 treatment-emergent adverse events were generally more common in the panitumumab group than in the control group (table 4). Differences between groups were significant for skin or eye toxicity ($p<0·0001$); hypomagnesaemia ($p<0·0001$); cardiac arrhythmias ($p=0·0474$); and diarrhoea ($p=0·0175$). Grade 3 or 4 infusion reactions were rare (table 4). Serious adverse events occurred in 157 (48%) of 325 patients in the panitumumab group included in the safety analyses and 139 (43%) of 325 in the control group. Adverse events resulting in discontinuation of panitumumab or chemotherapy, or both, or removal from the study occurred in 91 patients (28%) in the panitumumab group and 78 patients (24%) in the control group. Of these patients, 69 patients in the panitumumab group and 59 in the control group discontinued because of treatment-related toxicity.

Overall, 48 (15%) of the 325 patients in the panitumumab group and 41 (13%) of 325 in the control group included in safety analyses had on-treatment fatal adverse events. Death and disease progression occurred simultaneously in 12 patients in the panitumumab group and 17 patients in the control group. Other fatal adverse events were cardiac events (eight patients [2%] in the panitumumab group; seven [2%] in the control group), sepsis or febrile neutropenia (four [1%]; three [1%]), and haemorrhage (two [1%]; five [2%]). By investigator attribution, treatment-related deaths occurred in 14 patients (4%) in the panitumumab group and eight (2%) in the control group. Five patients (2%) had fatal adverse events that were attributed to panitumumab by the investigators: myocardial infarction, cardiac failure, cerebrovascular accident, acute renal failure, and haemorrhagic diarrhoea.

| | Panitumumab group (n=325) | | Control group (n=325) | |
|--|---------------------------|----------|-----------------------|----------|
| | Grade 3 or 4 | Grade 4 | Grade 3 or 4 | Grade 4 |
| Patients with any event | 219 (67%) | 96 (30%) | 214 (66%) | 81 (25) |
| Adverse events of interest | | | | |
| Skin or eyes, or both* | 62 (19%) | 5 (2%) | 6 (2%) | 0 |
| Hypomagnesaemia | 40 (12%) | 15 (5%) | 12 (4%) | 4 (1%) |
| Hypokalaemia | 33 (10%) | 9 (3%) | 23 (7%) | 10 (3%) |
| Stomatitis or oral mucositis | 29 (9%) | 2 (1%) | 28 (9%) | 2 (1%) |
| Cardiac arrhythmias | 19 (6%) | 3 (1%) | 8 (2%) | 5 (2%) |
| Dehydration | 16 (5%) | 2 (1%) | 7 (2%) | 0 |
| Diarrhoea | 15 (5%) | 1 (<1%) | 4 (1%) | 1 (<1%) |
| Venous embolic and thrombotic events | 13 (4%) | 8 (2%) | 6 (2%) | 4 (1%) |
| Acute renal failure | 10 (3%) | 3 (1%) | 11 (3%) | 1 (<1%) |
| Hypocalcaemia | 8 (2%) | 5 (2%) | 7 (2%) | 2 (1%) |
| Embolic and thrombotic events (unspecified or mixed vessel type) | 7 (2%) | 3 (1%) | 5 (2%) | 1 (<1%) |
| Arterial embolic and thrombotic events | 5 (2%) | 3 (1%) | 1 (<1%) | 1 (<1%) |
| Infusion reaction† | 2 (1%) | 0 | 0 | 0 |
| Ischaemic heart disease | 2 (1%) | 0 | 0 | 0 |
| Interstitial lung disease | 1 (<1%) | 1 (<1%) | 1 (<1%) | 0 |
| Severe cutaneous adverse reactions | 1 (<1%) | 1 (<1%) | 0 | 0 |
| Impaired or delayed wound healing | 0 | 0 | 1 (<1%) | 1 (<1%) |
| Haematological toxicity | 141 (43%) | 64 (20%) | 147 (45%) | 55 (17%) |
| Neutropenia | 103 (32%) | 43 (13%) | 106 (33%) | 40 (12%) |
| Anaemia | 39 (12%) | 5 (2%) | 47 (14%) | 5 (2%) |
| Thrombocytopenia | 21 (6%) | 9 (3%) | 25 (8%) | 8 (2%) |
| Febrile neutropenia | 20 (6%) | 12 (4%) | 17 (5%) | 6 (2%) |

Adverse events were coded using Medical Dictionary for Regulatory Activities (version 13.0) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), with the exception of some dermatological or skin adverse events that were graded with modifications to the criteria. *Includes preferred terms considered related to skin and eye toxicity. †Per US prescribing information.

Table 4: Treatment-emergent adverse events in the safety analyses

Fatal adverse events within the first 30 days of treatment occurred in 14 patients (4%) in the panitumumab group and 13 patients (4%) in the control group.

Of 298 patients who received panitumumab and for whom serum samples were available for testing, three (1%) developed anti-panitumumab antibodies. However, no anti-panitumumab-neutralising antibodies were detected.

Fixed-formalin paraffin-embedded tumour samples were available for assessment of p16 status for 443 (67%)

of 657 patients, yielding 1083 evaluable tumour cores. 99 (22%) of these 443 had p16-positive tumours and 344 (78%) had p16-negative tumours (table 5, appendix). The cumulative frequency distribution of p16-positive samples is shown in the appendix. The proportion of patients with p16-positive tumours was similar in the two

groups: 57 (24%) of 236 in the panitumumab group, and 42 (20%) of 207 in the control group (table 4). Many p16-positive patients had oropharyngeal tumours (table 4). The proportions of patients with different sites of tumour origin were generally consistent between patients who could and could not be assessed for p16 status (table 4). Demographic and baseline characteristics were generally balanced between treatment groups in p16-negative and p16-positive patients (data not shown). Furthermore, the proportions of patients who had previously received platinum-based chemotherapy differed between groups for both p16-negative (73 [41%] of 179 in the panitumumab group vs 55 [33%] of 165 in the control group) and p16-positive patients (21 [37%] of 57 patients vs 21 [50%] of 42).

Median overall survival in patients with p16-negative tumours was longer in the panitumumab group than in the control group, but not in those with p16-positive tumours (figure 5, table 6). Similarly, median PFS in patients with p-16 negative tumours was longer in the panitumumab group than in the control group, but not in those with p16-positive tumours (figure 5, table 6).

| | Assessable for p16 (n=443) | Not assessable for p16 (n=214) | p16 positive (n=99) | | p16 negative (n=344) | |
|-------------|----------------------------|--------------------------------|--------------------------|----------------------|---------------------------|-----------------------|
| | | | Panitumumab group (n=57) | Control group (n=42) | Panitumumab group (n=179) | Control group (n=165) |
| Hypopharynx | 61 (14%) | 28 (13%) | 5 (9%) | 3 (7%) | 34 (19%) | 19 (12%) |
| Oral cavity | 119 (27%) | 72 (34%) | 12 (21%) | 6 (14%) | 49 (27%) | 52 (32%) |
| Larynx | 137 (31%) | 58 (27%) | 16 (28%) | 10 (24%) | 58 (32%) | 53 (32%) |
| Oropharynx | 126 (28%) | 56 (26%) | 24 (42%) | 23 (55%) | 38 (21%) | 41 (25%) |

p16=p16-INK4A.

Table 5: Primary tumour site by p16 status

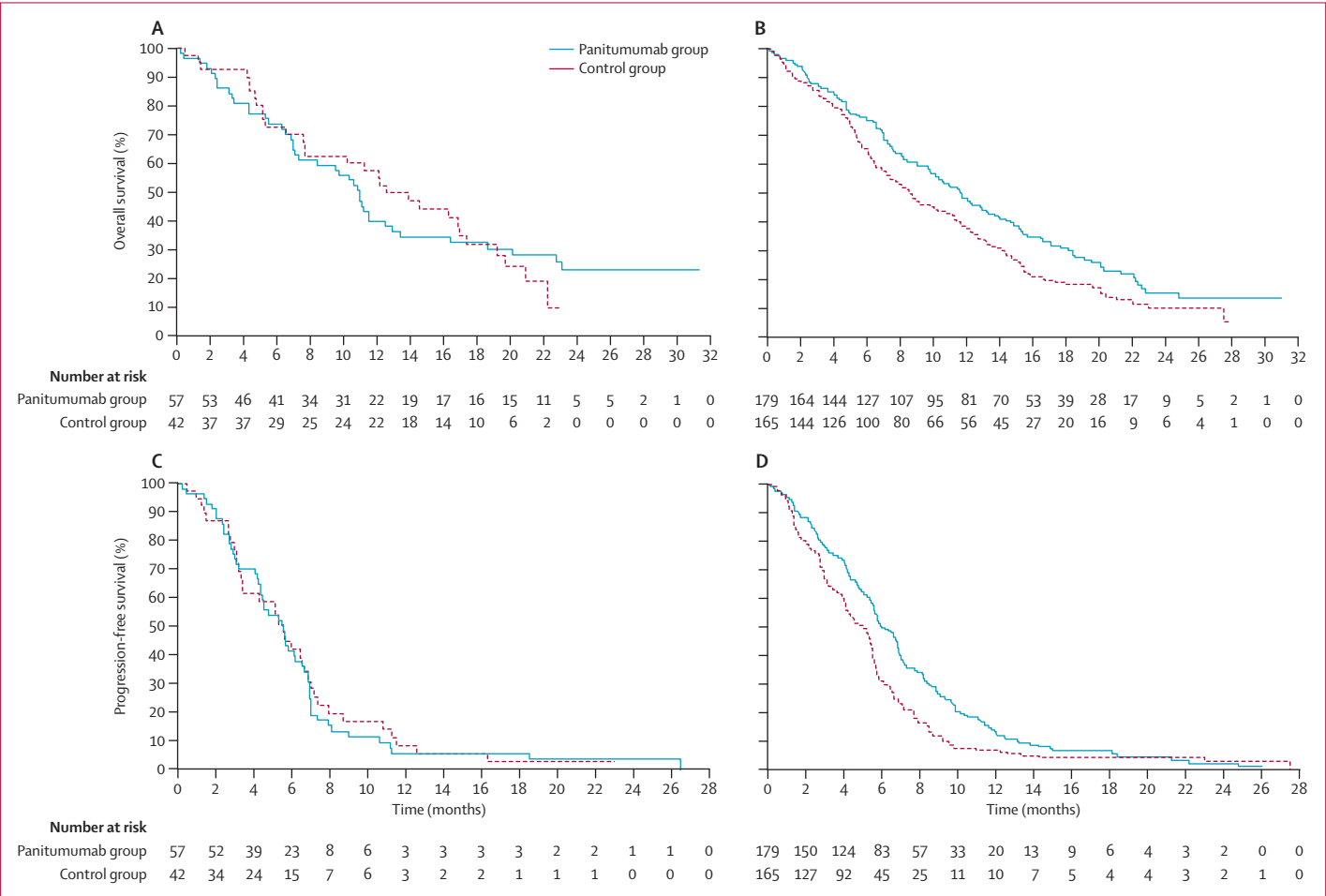


Figure 5: Overall and progression-free survival by p16 status
Overall survival in p16-positive (A) and p16-negative (B) patients. Progression-free survival in p16-positive (C) and p16-negative (D) patients. p16=p16-INK4A.

| | p16-positive patients | | | | p16-negative patients | | | |
|------------------------------------|-----------------------|-----------------|------------------|------------------|-----------------------|----------------|------------------|------------------|
| | Panitumumab group | Control group | Hazard ratio | Log-rank p value | Panitumumab group | Control group | Hazard ratio | Log-rank p value |
| Died | 42/57 (74%) | 30/42 (71%) | .. | .. | 133/179 (74%) | 133/165 (81%) | .. | .. |
| Overall survival (months) | 11.0 (7.3–12.9) | 12.6 (7.7–17.4) | 1.00 (0.62–1.61) | 0.998 | 11.7 (9.7–13.7) | 8.6 (6.9–11.1) | 0.73 (0.58–0.93) | 0.0115 |
| Progressed | 54/57 (95%) | 36/42 (86%) | .. | .. | 160/179 (89%) | 148/165 (90%) | .. | .. |
| Progression-free survival (months) | 5.6 (4.4–6.5) | 5.5 (3.4–6.7) | 1.08 (0.71–1.65) | 0.730 | 6.0 (5.6–6.9) | 5.1 (4.1–5.5) | 0.69 (0.55–0.87) | 0.0013 |

Data are n/N (%), median (95% CI), or hazard ratio (95% CI), unless otherwise stated.

Table 6: Overall and progression-free survival in the two treatment groups by p16 status

Of patients in the control group, those who were p16 positive had numerically, but not statistically significantly, longer median overall survival than did those who were p16 negative (12.6 months [7.7–17.4] vs 8.6 months [6.9–11.1]; HR 0.70, 95% CI 0.47–1.04; figure 6). Toxicity was generally similar between p16-negative and p16-positive patients, and between patients of different p16 status in the two treatment groups (appendix).

Discussion

SPECTRUM was a global study of a geographically diverse population of patients with wide variation in previous treatment. The results show that the addition of panitumumab to a regimen of cisplatin and fluorouracil does not significantly improve overall survival of patients with recurrent or metastatic SCCHN. By contrast, both progression-free survival and frequency of objective response were significantly improved by the addition of panitumumab, confirming its antitumour activity in SCCHN. Furthermore, in a prospectively defined retrospective analysis of p16 tumour status, we showed that overall survival was longer for p16-positive patients than for p16-negative patients who received only cisplatin and fluorouracil, suggesting that p16 status could be used as a prognostic marker in recurrent or metastatic SCCHN. Notably, the addition of panitumumab to the regimen resulted in significant improvements in overall and progression-free survival in patients with p16-negative tumours, but not in those with p16-positive tumours.

Two features of the primary analysis are noteworthy. First, median overall survival in both groups was longer than in two randomised studies.^{6,9} Median overall survival and progression-free survival in the group given cisplatin and fluorouracil alone were unexpectedly better than those in the previous studies (overall survival range 7.4–8.0 months; progression-free survival 2.7–3.3 months).^{6,9} Second, we recorded regional variation in the effect of panitumumab on overall survival, which potentially affected the aggregate results. The inclusion of patients from the Asia-Pacific region (who had fairly long overall survival) might account, at least partly, for the extended overall survival in the control

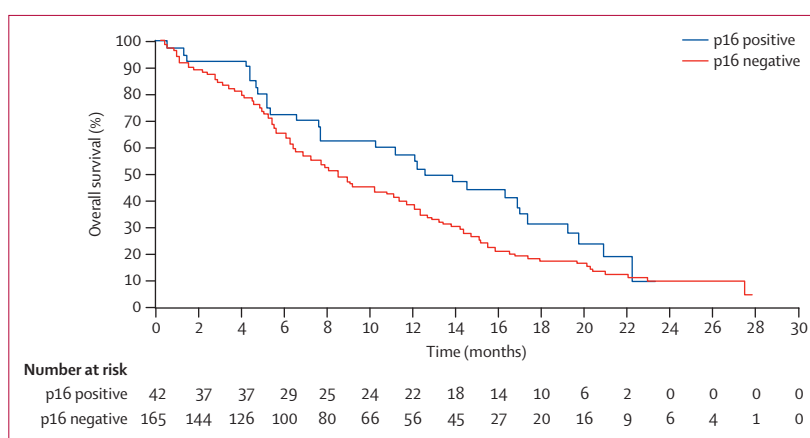


Figure 6: Overall survival in control group by p16 status
p16=p16-INK4A.

group compared with that in EXTREME⁹ (9.0 months vs 7.4 months).

We showed numerically, but not significantly, longer overall survival in the group given panitumumab for most subgroups. We recorded suggestions of increased benefits in subgroups known to have poor outlooks, such as those who had greater than 5% weight loss, previous platinum exposure, and moderately and well differentiated tumour subtypes. Progression-free survival was longer for patients who received panitumumab in most subgroups. The univariate and multivariate prognostic factors for overall survival identified in our study (performance status at study entry, weight loss, and previous platinum chemotherapy) were consistent with those previously reported by Argiris and colleagues.³⁵

The HPV analysis, in which p16 immunohistochemistry was used as a surrogate marker, showed that a p16-positive status was a prognostic factor. This finding is especially noteworthy because it extends results of previous studies in which tumour HPV status was shown to have prognostic value in patients with locoregionally advanced oropharyngeal SCCHN treated with chemotherapy or radiotherapy, or both.^{11–16} In our study, about half of p16-positive tumours were oropharyngeal, and the rest of p16-positive patients had laryngeal,

hypopharyngeal, and oral tumours, which is consistent with previous findings.^{36,37} The relative importance of HPV status in different SCCHN sites of origin remains to be defined in future clinical investigation. The proportion of p16-positive patients defined with our prespecified definition of strong and diffuse nuclear and cytoplasmic staining in at least 10% of tumour cells was also consistent with previous studies;^{36,37} results were similar when alternative cutoffs were used.

Notably, we showed that tumour p16 status might be a predictive biomarker for overall and progression-free survival in patients with recurrent or metastatic SCCHN treated with an anti-EGFR monoclonal antibody combined with chemotherapy. Furthermore, our results suggest that, in addition to the apparent effects of regional variation, variation in tumour p16 status could have affected the aggregate outcome results. The randomisation stratification of patients by combined tumour site (hypopharynx or oral cavity vs oropharynx or larynx) might have resulted in unequal stratification of patients with p16-positive tumours (most of whom had oropharyngeal tumours) between the two groups.

Our results raise important questions about tumour HPV status as a potential predictive biomarker in recurrent or metastatic SCCHN. SCCHN associated with HPV infection seems to be a biologically distinct subset of SCCHN, particularly with regard to differences in genetic alterations between HPV-positive and HPV-negative

disease.^{11,13,17,18} When tested as a specific immunohistochemical marker for HPV oncogene expression, p16 with a 10% cutoff is robust,³⁸ and has high concordance with high-risk HPV DNA, RNA, and E6 and E7 gene expression.^{39–41} Immunohistochemical detection of p16 has been successfully used in several clinical studies of patients with SCCHN as a screening marker to estimate HPV status.^{12,41–43} However, genetic differences between SCCHN types might affect the predictive ability of p16 as a biomarker.⁴⁴ We assessed p16 status as a biomarker by tumour site of origin. In view of the number of patients with each of the tumour types in our study, further research will be required to resolve the issue of genetic variation.

The results for overall survival in our primary analysis are surprising when compared with the phase 3 EXTREME study,⁹ in which overall survival was improved in patients who received cetuximab plus cisplatin or carboplatin and fluorouracil compared with those who did not receive cetuximab (10·1 vs 7·4 months; HR 0·80; $p=0·04$). Although heterogeneity in populations of patients makes comparisons between trials difficult, differences between the two studies in design and patient eligibility criteria could explain, at least partly, the varying findings. First, in the EXTREME study,⁹ continuation of cetuximab monotherapy after six cycles of chemotherapy was mandatory for patients who had not experienced disease progression, whereas in our trial, continuation of panitumumab monotherapy was optional.

Second, treatment received before enrolment differed greatly between the two studies (previous chemotherapy: 81% in our study vs 38% in EXTREME⁹). In our study, patients were not stratified by type of previous treatment, which also varied by region. Moreover, patients in EXTREME were allowed to receive either cisplatin or carboplatin from enrolment, whereas in our study, patients had to begin cisplatin and could only switch to carboplatin for reduced creatinine clearance (<50 mL/min) or grade 2 neurotoxicity. This requirement could have resulted in enrolment of a population with improved performance status, and therefore longer overall survival, compared with EXTREME.⁹

Third, in the EXTREME study,⁹ most patients were recruited from western Europe, whereas we recruited worldwide, with a third of patients from western Europe. In a subgroup analysis, we showed that overall survival was longer in patients from western Europe who received panitumumab than in those who did not.

Fourth, overall survival, but not progression-free survival, in our trial might have been confounded by treatment given after progression, including cytotoxic chemotherapy and targeted agents. Although roughly 5% of patients who received panitumumab plus chemotherapy and 9% of those who received chemotherapy alone received subsequent anti-EGFR targeted therapy for disease progression, the fairly infrequent crossover suggests that this potential confounder had a small effect. Finally, unlike in

Panel: Research in context

Systematic review

We did not do a formal systematic analysis before the start of our trial. We carefully reviewed reports of clinical trials assessing platinum-based chemotherapy treatment in recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) that were identified by a search of PubMed and abstracts from international clinical oncology meetings. The review showed that overall survival in this population remains poor despite presently available treatments and that anti-EGFR agents might have activity in this setting. On the basis of this review and discussions with researchers and clinical oncologists, improvement in overall response and overall survival was evidently a realistic goal for a clinical trial in this population of patients.

Interpretation

As far as we are aware, SPECTRUM is the largest global study of an EGFR inhibitor in combination with platinum and high-intensity infusional fluorouracil chemotherapy in a diverse population of patients with recurrent or metastatic SCCHN. Overall survival did not significantly improve with the addition of panitumumab to the chemotherapy regimen, but we did record improvements in progression-free survival and objective response. Furthermore, in a retrospective analysis, a negative tumour human papillomavirus status, assessed by p16 immunohistochemistry, predicted overall and progression-free survival after treatment with cisplatin and fluorouracil plus panitumumab. Moreover, a p16-positive status was a favourable prognostic marker in patients who received only chemotherapy, suggesting a potential prognostic effect in this population of patients. Our results indicate that tumour p16 status, regional differences in overall survival, and other factors (eg, the intensity and amount of previous treatment) might be important considerations in the design of future global trials in recurrent or metastatic SCCHN.

EXTREME,⁹ we did not insist that all patients had to have disease that could be measured with RECIST at enrolment, which was appropriate because the primary endpoint was overall survival and means the results can be generalised to a broad population.

Notably, overall survival of p16-negative patients in our study was longer than that in EXTREME (10·1 months in group given chemotherapy plus cetuximab; 7·4 months in group given chemotherapy alone).⁹ The results of a retrospective analysis of tumour p16 status in EXTREME,⁴⁵ which are qualitatively different from ours, suggested that the survival benefit of cetuximab treatment was independent of tumour p16 status. However, only 44 (12%) of 381 assessable patients in EXTREME were identified as being p16 positive, which could have restricted the ability to draw meaningful conclusions about the outcomes in these patients. Nevertheless, these contradictory findings underscore the necessity to further assess the role of HPV in the setting of recurrent or metastatic disease (panel). Prospective assessment will be necessary to confirm tumour HPV status as a predictive biomarker for anti-EGFR therapy in recurrent or metastatic SCCHN.

We noted no unexpected safety findings. Frequency of skin toxicity, hypomagnesaemia, hypokalaemia, diarrhoea, and dehydration were generally consistent with that reported with other anti-EGFR monoclonal antibodies in patients with recurrent or metastatic SCCHN.^{9,46} These events have also been reported in patients receiving panitumumab with or without chemotherapy for metastatic colorectal cancer.^{47–49} The subjectivity of grading of skin toxicity, the use of different grading scales, and differences in the descriptive terms for skin toxicity between our trial and EXTREME⁹ make comparisons of the frequency of skin toxicity between the two studies difficult.

Compliance with chemotherapy in both groups in our study was good. Exposure to cisplatin or carboplatin was similar across the groups, and exposure to fluorouracil was moderately greater in the group that received chemotherapy plus panitumumab (probably because of the reduced disease progression rate).

In conclusion, the addition of panitumumab to chemotherapy did not improve overall survival of patients with recurrent or metastatic SCCHN. However, significant improvements were noted with the addition of panitumumab in terms of PFS and the number of patients who achieved an objective response. Subgroup analyses suggested that clinical benefit may have been greater among certain patient subgroups, although these data should be interpreted with care given the small size of some of the groups. Furthermore, our retrospective analyses suggested that tumour p16 status might have both prognostic and predictive value in patients with recurrent or metastatic SCCHN treated with panitumumab combined with chemotherapy, although these findings require further validation.

Contributors

JBV did the literature search for the study. JS-W, ID, LL, CV, PF, SR, MT, VRP, SF, CRB, and BAB collected data. JS-W, EW, PF, SR, MT, VRP, SF, CRB, AAF, BNS, and BAB enrolled patients and obtained study materials. JBV, JS-W, and ZP designed the study. JBV, JS-W, LL, EW, MT, VRP, SF, CRB, BNS, KSO, ZP, and BAB analysed and interpreted data. JBV, JS-W, EW, CV, PF, SR, MT, SF, CRB, AAF, BNS, KSO, ZP, and BAB wrote the report. KS participated in the steering committee. KSO developed and implemented the biomarker testing strategy. BAB provided administrative support and helped to obtain financial support for the study.

Conflicts of interest

JBV has served as a paid consultant for Amgen Inc and has received honoraria from Amgen Inc for scientific presentations at satellite symposia and for advisory boards. JS-W has received honoraria for advisory boards and speaking, travel support, and research funding from Amgen Inc, Roche, Eli Lilly, Boehringer Ingelheim, and Merck Serono. LL has received honoraria for advisory boards from Amgen Inc. MT has received research funding from Eisai and Yakult. SF has served as a paid consultant for, and has received honoraria for participating in a steering committee, from Amgen Inc. KSO, ZP, and BAB are employees of, and own stock in, Amgen Inc. The other authors declare that they have no conflicts of interest.

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